Remarks

Reconsideration of this Application is respectfully requested.

Claims 166, 168, 170, 177 and 247 are pending in the application, with claim 166 being the independent claim. Claim 170 has been amended to clarify the claimed invention.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102(e)

Claims 170 and 247 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Chien *et al.* (U.S. Pat. No. 6,150,087). (Office Action, page 2.) Applicants respectfully traverse the rejection.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); *see also* MPEP § 2131.

Claim 170 as amended is directed to a CTL/HTL epitope conjugate, where the CTL epitope of the CTL/HTL epitope conjugate consists of the isolated peptide of claim 166, and where the CTL epitope is linked to *a non-HCV(Hepatitis C Virus) HTL epitope* either directly or via a spacer at the amino or carboxy terminus of the CTL peptide, where the spacer is no more than six residues in length. Thus, the recited conjugate contains three elements: (1) a CTL epitope; (2) an HTL epitope; and, optionally, (3) a spacer that is no more than six residues in length. The spacer is optional as the CTL

epitope can be linked to the HTL epitope directly or can be linked via a spacer. The recited CTL/HTL conjugate contains no additional elements other than those listed above. Claim 247 depends from claim 170, and therefore incorporates all of the limitations of claim 170.

The first element, the recited CTL epitope, *consists of* the isolated peptide of claim 166. The term "consisting of" is considered to be closed. *See Georgia-Pacific*, 195 F.3d at 1327-28; *see PPG Indus.*, 156 F.3d at 1354.. Thus, the CTL epitope of the recited CTL/HTL epitope conjugate contains only the sequence of the isolated peptide of claim 166, and no additional features. The second element, the HTL epitope, is a *non-HCV HTL epitope*. Thus, the HTL epitope *does not contain HCV sequence* because it is a *non-HCV HTL epitope*. The third element, which is optional, is a spacer sequence no more than six residues in length.

Chien does not disclose a CTL/HTL conjugate as required by Applicants' claimed invention. Chien discloses *an HCV sequence 50 amino acids in length* (AA1850-AA1900) which *comprises* the sequence GVAGALVAFK. (*See* Chien, col. 27, second paragraph). Chien does not disclose Applicants' claimed peptide, and therefore does not disclose the CTL epitope of Applicants' CTL/HTL epitope conjugate. The 50 amino acid sequence (AA1850-AA1900) disclosed in Chien contains 40 additional amino acid residues *corresponding to HCV sequence*. Thus, this 50 amino acid sequence does not disclose the *non-HCV* HTL epitope as required by the claim.

Thus, Chien fails to teach every aspect of Applicants' claimed invention. Accordingly, Applicants respectfully assert that claims 170 and 247 are not anticipated by Chien and request that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

Claims 166, 168, 170, 177 and 247 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over Chien, in view of Berzofsky *et al.* (U.S. Pat. No. 5,980,899) and Guo *et al.* (*Nature 360*:364-366 (1992)). Applicants respectfully traverse the rejection.

The standard for obviousness is set forth in 35 U.S.C. §103 as follows:

> A patent may not be obtained though the invention is not identically disclosed as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

35 U.S.C. §103(a) (2000).

The United States Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966) factors provide a framework to make a determination of obviousness. Those factors are: 1) "the scope and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness (*KSR*, 127 S.Ct. at 1734 (*quoting Graham*, 383 U.S. at 17-18).)

The Supreme Court has recently stated that "[w]hen there is a design need or market pressure to solve a problem and there are a *finite number* of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known

options within his or her technical grasp. . . . [i]n that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *See KSR* at 17 (emphasis added).

In *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007), a post-*KSR* case, the Federal Circuit elaborated on the issue of obviousness where the prior art disclosed a large number of possible solutions. In its analysis, the Federal Circuit stated that

> Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. . . . Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Takeda, 492 F.3d at 1359. The present case is similar to the situation in *Takeda*. In this instance, the cited references, at best, provide an extremely large number of epitopes upon which one of ordinary skill in the art can apply certain screening criteria, where the screening criteria provide no guarantee that an immunogenic CTL epitope will in fact be selected.

Applicants note that Chien discloses over 180 different HCV fragments ranging in size up to 70 amino acids in length, and spanning a sequence that is nearly 3000 amino acids in length. Chien does not indicate whether any particular fragments are preferable to any others. Chien merely divides the larger approximately 3000 amino acid sequence into various smaller fragments. There are potentially hundreds of different immunogenic epitopes that could be selected within the larger approximately 3000 amino acid

sequence, and within all of the various smaller fragments. If one were guided to one particular fragment of the hundreds listed, one would be provided with a smaller source of potential CTL epitopes. However, this is not what Chien provides. Chien does not provide any guidance as to which particular fragment would be best suited to obtain an immunogenic HCV sequence. In fact, Chien states that "[i]t is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is not immunogenic." Chien, col. 27, lines 10-13. Furthermore, Chien, in discussing ways that one of ordinary skill in the art could apply techniques to identify potential immunogenic candidates, also notes that "[i]t is appreciated by those of skill in the art that such computer analysis of antigenicity does not always identify an epitope that actually exists, and can also incorrectly identify a region of the protein as containing an epitope." *Id.* at lines 4-8. Thus, Chien provides about 3000 amino acids of sequence from which an immunogenic peptide could be derived, but using the disclosure of Chien, it would not be at all predictable to arrive at Applicants' claimed peptide.

While the Examiner may now hone in on a particular fragment (AA1850-AA1900) using Applicants' claimed peptide as a starting point, this is applying hindsight reasoning in selecting which particular fragment, of the hundreds disclosed in Chien, to use as a starting point. There is nothing in Chien that points to the AA1850-AA1900 fragment in particular, and without the knowledge of Applicants' claimed peptide being a CTL epitope, nothing in Chien would lead to Applicants' elected peptide, let alone the AA1850-AA1900 fragment that *comprises* the peptide.

In *Takeda*, the Federal Circuit distinguished the facts of the case from those in another of their recently-decided cases, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). The Federal Circuit stated that in *Pfizer*, in contrast to *Takeda*, the "prior art provided 'ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate.' Here, the court found nothing in the prior art to narrow the possibilities of the lead compound to compound b." *Id.*

In the present case, none of the references cited by the Examiner provide the guidance as presented in *Pfizer* that would allow one of ordinary skill in the art to further narrow down the large number of possible HCV CTL epitopes that could be obtained. Applicants assert that it would have been unpredictable, in view of the cited art, to arrive at Applicants' claimed peptide. Thus, in view of *KSR* and the subsequent decisions of *Takeda* and *Pfizer*, the present invention is not rendered obvious by Chien in view of Berzofsky or Guo.

Chien, as discussed above, does not disclose every element of Applicants' claimed invention. This is supported by the Examiner's own statement that "Chien et al. do not teach the peptide of claim 166/168." (Office Action, page 4.) The Examiner further states that "[v]irtually any intact immunogenic molecule will contain at least one helper cell epitope." (*Id.*) The Examiner, however, has not provided any evidence to support this assertion. As noted above, the Chien reference in fact notes that "[i]t is to be understood that these peptides do not necessarily precisely map one epitope, but may also contain HCV sequence that is *not immunogenic*." Chien, col. 27, lines 10-13 (emphasis added).

The Examiner has also alleged that "the functional attributes of claim 166 would presumably be present in the peptide of Chien et al. in that said larger peptide would be processed in vivo to yield the peptide of claim 166." (Office Action, page 7.) The Examiner also has not provided any evidence to support this particular assertion.

Applicants have cited Yewdell, Eisenlohr and DelVal (Amendment and Reply of November 15, 2005, and Amendment and Reply dated August 29, 2005) in support of the proposition that it is difficult to identify exactly which specific peptides are capable of inducing an immune response within a given longer sequence. Applicants note that while flanking resides may be able to positively affect the presentation of an immunogenic peptide, Eisenlohr teaches that the addition of flanking residues can also destroy the antigenicity of a particular peptide. *See* Eishelohr, page 485, first paragraph. Therefore, an epitope embedded within a larger sequence may be processed differently, and thus have different immunogenicity than the same epitope free of flanking or surrounding amino acid residues. In view of Eisenlohr, the Examiner cannot simply assume that any longer fragment that is processed *in vivo* will predictably generate a smaller immunogenic peptide derived from that longer fragment.

The Examiner also states that

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Chen et al. teach an immunogenic HCV peptide containing GVAGALVAFK, whilst Berzofsky et al. teach that it is desireable to identify CTL epitopes found in HCV and Guo et al. teach that CTL recognize viral peptides complexed with MHC and that peptides which bind HL-Aw68 generally are 9 to 11 amino acids with a V at P2 (position 2) and a K at the c-terminal position.

(Office Action, page 4.)

While Berzofsky generally describes other regions of HCV, it does not provide any guidance with regard to which specific regions of the HCV genome necessarily contain good targets for CTL, nor does it contain any guidance to identify Applicants' claimed peptide. A prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *See* M.P.E.P. § 2141.02(VI) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983)); *see also Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 1093-94 (Fed. Cir. 1985) ("The well established rule of law is that each prior art reference must be evaluated as an entirety . . . ."). That is, "[t]here is no suggestion to combine . . . if a reference teaches away from its combination with another source." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999); *see also KSR* at 12 (reaffirming "the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious") (citing *United States v. Adams*, 383 U.S. 39, 51-52 (1966)).

Applicants' elected peptide, GVAGALVAFK, is neither discussed, nor described in Berzofsky. In addition, the peptides of Applicants' claimed invention are determined using techniques which do not rely on the amphipathicity algorithm of Berzofsky. Berzofsky does not disclose the techniques Applicants' utilized to identify candidate CTL epitopes. Therefore, at best, Berzofsky is an invitation to identify a peptide. Given the relatively large number of possible epitopes that could be identified within the HCV genome, the Berzofsky article, without more, cannot be viewed to provide a sufficient

reason to modify the art to arrive at Applicants' claimed invention. As such, Chien in view of Berzofsky does not render the claims obvious.

The Examiner has also alleged that Chien, in view of Berzofsky, and further in view of Guo allegedly renders the claims obvious. Guo generally describes how CTL recognize viral peptides complexed with MHC and that these peptides generally are 9 to 11 amino acids in length. Guo, page 364. While Guo discloses peptide sequences from several proteins including ribosomal 60S, human Hsp70, and influenza NP (Guo, Table 1), Guo does not contain any discussion regarding the identification of CTL epitopes within the HCV genome, nor does Guo disclose Applicants' elected peptide. The Examiner has also alleged that:

> Applicants arguments also ignore the teachings of Guo et al. Guo et al. teach that CTL recognize viral peptides complexed with MCH. Guo et al. teach that said peptides which bind HLA-Aw68 generally are 9 to 11 amino acids with a V at P2 and a K at the c-terminal position.

(Office Action, page 7 (parentheticals omitted).) Applicants respectfully note that even applying the teachings of Guo to Chien, one of ordinary skill in the art would arrive at a large number of possible candidates considering the large number of fragments, and the approximately 3000 amino acid HCV sequence disclosed in Chien. Thus, in view of the cited art, one of ordinary skill in the art would not predictably arrive at Applicants' claimed peptide.

Finally, Applicants' have shown that the elected peptide GVAGALVAFK exhibits the strongest CTL-inducing response in transgenic mice as compared to any of the other peptides listed in Table XXIII and compared to any of the other peptides which share the same A3 motif. Applicants also point out that in Table XVI, Applicants'

elected peptide GVAGALVAFK exhibits one of the strongest binding affinities as compared to over 400 other peptides which share the same A3 motif.

Thus, the CTL-inducing and binding characteristics of the GVAGALVAFK peptide, as determined by Applicants, demonstrate that the GVAGALVAFK peptide has unexpected properties. In view of the improved binding properties of the GVAGALVAFK peptide as compared to over 400 other peptides sharing the same motif, and in view of the significantly greater CTL induction generated as compared to other peptides sharing the same motif, Applicants assert that evidence of nonobviousness and/or unexpected advantageous properties is present. It is the functional characteristic of the peptide, as determined by the Applicants, which renders the peptide to have an unexpected property, and thus renders the peptide non-obvious in view of the prior art.

While the Examiner has cited the MPEP in stating that the "[m]ere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention," (Office Action, page 7 citing *In re Wiseman*, 596 F.2d 1019 (CCPA 1979) Applicants point out that the elected peptide *was not in the prior art*. Thus, Applicants have not merely recognized latent properties in a prior art compound. In fact, Applicants have not only discovered a *novel* peptide - - GVAGALVAFK -- that would have been unpredictable to obtain from the extremely large number of candidates in the art, but have also determined that this peptide exhibits a superior property. Thus, Applicants selecting the novel GVAGALVAFK peptide out of numerous other possible candidates is nonobvious.

Accordingly, Chien, in view of Berzofsky, and further in view of Guo does not render the claimed invention obvious. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Mita Mukherjee
Agent for Applicants
Registration No. 54,325

Date: February 24, 2009

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600
944581_1.DOC